

# Arnold & Porter

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Via Hand Delivery

Ms. Susan Edwards  
Chief, Industry Guidance Branch  
U.S. Department of Health and Human Services  
Office of Inspector General  
Office of Counsel to the Inspector General  
Room 5527, Cohen Building  
330 Independence Avenue S.W.  
Washington, D.C. 20201

DHHS/OS/OIG  
OFFICE OF COUNSEL TO THE IG

2019 AUG 26 PM 2:32

Re: *Pfizer Inc. Request for Advisory Opinion Regarding a Program  
Designed to Enhance Patient Access to Vyndaqel® and Vyndamax™  
Through Copay Assistance*

Dear Ms. Edwards:

Pfizer Inc. (“Requestor”) submits this request for an advisory opinion approving a copay assistance program that would enable financially-disadvantaged federal healthcare beneficiaries to afford Requestor’s recently approved, life-extending breakthrough medication for a fatal rare disease known as transthyretin amyloid cardiomyopathy (“ATTR-CM”), which affects an estimated approximately 100,000 to 150,000 Americans.<sup>1</sup> Specifically, Requestor wishes to offer copay assistance to eligible Medicare Part D beneficiaries to help them pay the True Out-of-Pocket (“TrOOP”) costs required to reach the catastrophic phase of their Part D benefit, an amount that changes annually (\$5,100 in 2019; \$6,350 in 2020), and the 5% coinsurance required during the catastrophic phase of their Part D benefit. For the reasons outlined in this submission, the unique facts and circumstances presented by the disease and its treatment support an advisory opinion permitting Requestor to implement a well-designed and regulated copay assistance program.

Left untreated, ATTR-CM is a progressive, debilitating disease that inevitably results in heart failure and death, usually within three-to-five years of diagnosis. No approved pharmacological therapy existed to treat ATTR-CM until May 3, 2019, when the U.S. Food and Drug Administration (“FDA”) approved two formulations of the drug tafamidis, Vyndaqel® (tafamidis meglumine) and Vyndamax™ (tafamidis) (collectively, “tafamidis” or the “Medications”) as the first and only medicines for the treatment of

<sup>1</sup> This prevalence estimate and all other estimates in this document are based on currently available information, and may change over time as knowledge of ATTR-CM improves. The current estimated ATTR-CM diagnosis rate is approximately two percent.

ATTR-CM in adults. The pivotal phase 3 trial demonstrated that Vyndaqel significantly reduced all-cause mortality (by 30%), decreased the frequency of cardiovascular-related hospitalizations (by 32%), and slowed the decline in functional status and quality of life, as compared with placebo. Extrapolation of this study data also indicates an approximately 18-month increase in median overall survival between patients on tafamidis versus placebo.<sup>2</sup> The director of the Division of Cardiovascular and Renal Drugs in the FDA's Center for Drug Evaluation and Research described the Medications as "an important advancement in the treatment of the cardiomyopathy caused by transthyretin-mediated amyloidosis."<sup>3</sup>

The Medications have a list price of \$225,000 for a one-year course of treatment. As explained in this submission, the Medications' price is well below comparable novel therapies approved to treat other rare diseases. That price, moreover, is consistent with the Medications' strong efficacy and safety profile, its slowing of the decline in functional status and quality of life, and the relatively small orphan population of patients with ATTR-CM. The Medications also cost substantially less than heart and liver transplants, which are other potential options for patients with ATTR-CM.

Requestor is committed to helping ensure that all patients suffering from ATTR-CM can afford this breakthrough therapy, while also complying fully with the anti-kickback statute ("AKS") and the beneficiary inducement statute ("BIS"). Taking into account Requestor's existing copay program for commercially insured patients, Requestor expects that the out-of-pocket cost for patients with non-Medicare insurance will be less than \$55 per month for the Medications. But unless Requestor is permitted to offer copay assistance to Medicare Part D beneficiaries, many elderly, middle-class patients suffering from ATTR-CM will be unable to afford this critical therapy. Under the Medicare Part D benefit structure, a patient must pay approximately \$13,000 in annual out-of-pocket expenditures for the Medications, based on the cost-sharing requirements under the various Part D phases (*i.e.*, deductible, initial benefit limit, coverage gap and catastrophic). These coinsurance amounts typically are based on the list price of the drug and do not include rebates negotiated by the Part D plan with manufacturers. Even if Pfizer cut the list price of the Medications in half, the Part D benefit structure still would result in patient out-of-pocket costs that are unaffordable for a significant number of Medicare beneficiaries. And while Requestor currently offers a generous free drug program through its patient assistance program, which is open to both uninsured and underinsured financially-disadvantaged patients, that program cannot be sustainably extended to all Medicare

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<sup>2</sup> During the 30 months of the study, the median overall survival was not reached in either the pooled tafamidis or placebo treatment groups as there were not enough deaths occurring within that time horizon. Therefore, a statistical method that relies on an extrapolation procedure was applied, as is often done to provide insight into treatment outcomes in the future.

<sup>3</sup> See FDA News Release, *FDA approves new treatments for heart disease caused by a serious rare disease, transthyretin mediated amyloidosis* (May 6, 2019), available at <https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatments-heart-disease-caused-serious-rare-disease-transthyretin-mediated>.

beneficiaries who would be unable to afford the annual out-of-pocket cost of the Medications.

To overcome that significant financial barrier to accessing this breakthrough therapy, Requestor proposes to provide copay assistance directly to eligible Medicare Part D beneficiaries prescribed the Medications for an on-label indication and who demonstrate financial need (the “Copay Assistance Program”). Assistance would be provided through a coupon to significantly reduce required copays/coinsurance collected by specialty pharmacies that fill prescriptions for the Medications. In order to ensure that the program achieves its patient access and affordability objectives, Requestor’s assistance would count towards the patient’s TrOOP.

Requestor supports the mission of the AKS and the BIS to prevent fraud and abuse in the health care system, and nothing in this request should be viewed as an effort to undermine these statutes. Requestor believes, however, that the proposed Copay Assistance Program falls within a statutory exception that expressly exempts copay waivers from the reach of these statutes in defined circumstances. Although OIG previously has excluded pharmaceutical manufacturers from relying upon that exemption, Requestor respectfully submits that the statutory and regulatory texts do not support that interpretation in the unique and limited circumstances of Requestor’s proposed program.

Furthermore, Requestor believes that its proposed arrangement does not constitute “inducement” for the purposes of the AKS or the BIS. The proposed Copay Assistance Program provides no financial incentive to physicians to favor the Medications. Prescribers will exercise independent medical judgment on whether a patient should use the Medications based on the Medications’ efficacy and safety for treating ATTR-CM, after objective diagnosis of that condition and based on each patient’s medical profile and treatment needs. The only purpose of the proposed Copay Assistance Program is to help patients who suffer from ATTR-CM gain access to the only approved treatment for that fatal condition. Because no alternative pharmacologic therapies have been approved (and organ transplant is both far more expensive and rarely a viable option), the proposed arrangement presents no risk of inappropriately steering patients toward the Medications or improperly inducing prescriptions for the Medications.<sup>4</sup>

Even if OIG believes that the proposed arrangement implicates the AKS or the BIS, the unique factors presented here support a finding that the proposed arrangement presents a low risk of fraud and abuse and therefore warrants a favorable exercise of HHS OIG’s enforcement discretion. The proposed Copay Assistance Program would expand patient access and encourage appropriate use of the Medications without risk of overuse or improper influence over prescribing decisions. Most importantly, the proposed arrangement would help ensure that all patients with ATTR-CM have access to the best available pharmacological treatment, regardless of their financial resources—an outcome that advances Medicare Part D’s most basic purpose. Accordingly, OIG should provide a

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<sup>4</sup> FDA approval for any competitor products is not expected until at least 2021.

safe harbor because the Copay Assistance Program would not pose risk of fraud and abuse and would further important health policy objectives.

Important constitutional considerations also warrant HHS OIG's approval of the proposed arrangement. A decision that bars the proposed Copay Assistance Program would arbitrarily deny access to the Medications based solely on a federal beneficiaries' age and socio-economic status in a manner that raises serious equal protection concerns. An advisory opinion providing Requestor with a safe harbor to proceed with the proposed arrangement would avoid this constitutional question.

For these reasons, pursuant to Section 1128D of the Social Security Act ("SSA" or the "Act") and 42 C.F.R. § 1008 *et seq.*, we request that OIG issue an advisory opinion approving Requestor's proposed Copay Assistance Program to assist ATTR-CM patients.<sup>5</sup> Specifically, Requestor respectfully seeks an advisory opinion that the proposed arrangement would not constitute:

- prohibited remuneration or inducement within the meaning of the AKS and BIS;
- grounds for the imposition of sanctions under the BIS; or
- a basis to impose sanctions under SSA §§ 1128(b)(7) or 1128A(a)(7) as they relate to the AKS.

If OIG believes that the Copay Assistance Program involves prohibited remuneration implicating the AKS and the BIS, Requestor would be interested in engaging in collaborative dialogue with OIG to discuss OIG's position and to identify potential modifications to the proposed program that would obviate those concerns. Alternatively, Requestor respectfully requests that OIG issue an advisory opinion establishing a safe harbor for the Copay Assistance Program based on prudential factors. Requestor believes that the unique facts relevant to the Medications and the patient population that can benefit for this important breakthrough therapy warrant careful consideration.

In light of patients' urgent need for access to the Medications, Requestor respectfully asks that OIG provide a response within 60 days of this submission confirming that the Copay Assistance Program does not involve prohibited remuneration or establishing a safe harbor for the arrangement. As noted, Requestor is prepared to work collaboratively with OIG to find a means of ensuring access to the Medications for qualifying patients.

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<sup>5</sup> Requestor would proceed in good faith with the program described herein if OIG issues a favorable advisory opinion.

## I. ADMINISTRATIVE MATTERS

At the outset, we address the various administrative requirements outlined in 42 C.F.R. § 1008 *et seq.*:

- Pursuant to 42 C.F.R. §§ 1008.11 and 1008.36(b)(1), the entity making this request is a party to the arrangement. Requestor's full name and corporate office address are as follows:

Pfizer Inc.  
235 East 42nd Street  
New York, NY 10017

- Pursuant to 42 C.F.R. § 1008.15(a), this request relates to a program that Requestor plans in good faith to undertake. Pursuant to 42 C.F.R. § 1008.38(b), the required signed certification by Requestor that the program is one that Requestor in good faith plans to undertake may be found at Exhibit A.
- Pursuant to 42 C.F.R. § 1008.15(c)(2), to the best knowledge of Requestor, this request does not involve a question regarding the same or substantially the same course of action that is under investigation or is or has been the subject of a proceeding involving the Department of Health and Human Services or another governmental agency.
- Pursuant to 42 C.F.R. § 1008.31, Requestor acknowledges the requirement to make payment for the requested Advisory Opinion to the Treasury of the United States, as directed by OIG.
- Pursuant to 42 C.F.R. § 1008.36(a), this submission contains one (1) original and two (2) copies of the Advisory Opinion request and all supporting materials.
- Pursuant to 42 C.F.R. § 1008.36(b)(2), the contact person who will be available to discuss this request is:

Jeffrey L. Handwerker  
Arnold & Porter Kaye Scholer LLP  
601 Massachusetts Avenue, NW  
Washington, D.C. 20001-3743  
Direct Dial: 202-942-6103  
E-Mail: Jeffrey.Handwerker@arnoldporter.com

- Pursuant to 42 C.F.R. § 1008.36(b)(3), Requestor declares that the subject of this request falls under the subject matter categories described at 42 C.F.R. § 1008.5(a)(1) and (a)(5). Specifically, we request OIG's opinion on whether the proposed arrangement constitutes (1) prohibited remuneration within the meaning of SSA § 1128B(b), and (2) grounds for the imposition of sanctions under SSA §

1128(b)(7) or 1128A(a)(7) (as they relate to the AKS) or 1128A(a)(5) (regarding beneficiary inducements).

- Pursuant to 42 C.F.R. § 1008.36(b)(4), Requestor declares that all relevant information bearing on the arrangement for which an Advisory Opinion is requested is included in this letter.
- Pursuant to 42 C.F.R. § 1008.36(b)(6), the required declaration may be found at Exhibit B.
- Pursuant to 42 C.F.R. § 1008.36(b)(7), Requestor's Employer Identification Number ("EIN") for tax purposes is 13-5315170.
- Pursuant to 42 C.F.R. § 1008.37, Exhibit C contains a full and complete list of each entity controlled or owned by Requestor. No person or entity owns more than 10% of Requestor's shares.
- Pursuant to 42 C.F.R. § 1008.38(a), a certification concerning the truth and accuracy of the information in this request is attached at Exhibit A.
- Pursuant to 42 C.F.R. § 1008.36(b)(4)(v), a designation of trade secrets or confidential commercial or financial information is attached at Exhibit D.

## II. RELEVANT BACKGROUND

### A. ATTR-CM Is a Rare, Deadly Disease Affecting the Heart

ATTR-CM is a rare, progressive disease caused by deposition of transthyretin amyloid fibrils in the heart. These fibrils build up in heart tissue, causing damage to cells and limiting the heart's ability to pump blood to the lungs and throughout the body. As more amyloid is deposited, in a process called amyloidosis, the heart progressively stiffens and ultimately fails.

In early stages of the disease, patients typically experience heart failure symptoms, such as shortness of breath and fatigue. As the symptoms worsen over time, many patients experience severe shortness of breath, fatigue with minimal activity, and cardiac arrhythmias (abnormal heart rhythms). In latter stages, most patients have difficulty performing even the most basic activities of daily living and frequently require full time care.<sup>6</sup> Patients usually die within three-to-five years of receiving an ATTR-CM diagnosis.<sup>7</sup> Their stories are heartbreakng.<sup>8</sup>

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<sup>6</sup> See [http://amyloidosisupport.org/support\\_groups/fam\\_isabell\\_attr.pdf](http://amyloidosisupport.org/support_groups/fam_isabell_attr.pdf).

<sup>7</sup> See <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3501197/>.

<sup>8</sup> See, e.g., "With Hope for a Cure," <http://amyloidosis.org/proactive-3/>.

Before the Medications, no approved pharmacological treatments existed for ATTR-CM. A small number of ATTR-CM patients would undergo dual heart and liver transplants, in hopes of curing the disease, or at least improving their prognosis. These procedures have had some success, but limited application in practice, because most patients with ATTR-CM are too sick and have too many other medical problems to meet transplant criteria. Furthermore, the cost of such transplant can easily be more than \$2 million.<sup>9</sup>

ATTR-CM can be an inherited condition (“hereditary” form), or it can occur spontaneously in elderly patients without a known predisposition (“wild type” form). The two forms of the disease have a similar presentation, though the disease may progress more quickly in those with the hereditary form. Diagnosis of ATTR-CM is made objectively by heart biopsy or nuclear scintigraphy (an imaging technology). In the United States, the majority of hereditary cases are caused by a specific gene mutation called Val122Ile. The Val122Ile mutation may be present in 3-4% of the African-American population, though it is estimated that less than 30% of those with the mutation will develop the disease. The wild-type form typically affects older, Caucasian men. Many of these patients are Medicare beneficiaries and have limited financial resources.

The precise number of people who suffer from ATTR-CM is unknown. However, it is estimated that approximately 100,000 to 150,000 Americans may have the disease.<sup>10</sup> Many of these patients remain misdiagnosed or undiagnosed.<sup>11</sup>

## B. The Medications Are the First and Only Drug Therapies Approved for ATTR-CM

On May 3, 2019, FDA approved the Medications for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. The Medications are the first and only medicines approved for treatment of ATTR-CM.

While the Medications are not a cure, they offer patients hope for a longer and better life and may provide a bridge to future therapies. The pivotal phase 3 trial demonstrated

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<sup>9</sup> See T. Scott Bentley, 2017 U.S. Organ and Tissue Transplant Cost Estimates and Discussion, Milliman Research Report (Aug. 2017), available at [http://www.milliman.com/insight/2017/2017-U\\_S\\_-organ-and-tissue-transplant-cost-estimates-and-discussion/](http://www.milliman.com/insight/2017/2017-U_S_-organ-and-tissue-transplant-cost-estimates-and-discussion/) for 2017 U.S. organ and tissue transplant cost estimates and discussion. The \$2 million estimate includes expenses associated with the pre-transplant hospitalization period, organ procurement, hospital transplant admission, physicians, 180-days post-transplant discharge, immunosuppressants, and other prescription medications. It does not reflect additional costs related to complications during or after the surgery, including serious risks such as kidney failure, organ rejection and death.

<sup>10</sup> See Dharmarajan K, Maurer MS. Transthyretin cardiac amyloidoses in older North Americans. J Am Geriatr Soc. 2012;60:765-774.doi: 10.1111/j.1532-5415.2011.03868.x; <https://www.ahajournals.org/doi/pdf/10.1161/CIRCHEARTFAILURE.116.003815>.

<sup>11</sup> Based on currently available information, Requestor understands that approximately two percent of this population are diagnosed with ATTR-CM. To mitigate these concerns, Requestor has launched a genetic testing and counseling program that is the subject of a separate advisory opinion request that Requestor filed on May 15, 2019.

that Vyndaqel significantly reduced all-cause mortality (by 30%) and decreased the frequency of cardiovascular-related hospitalizations (by 32%), as compared with placebo. Extrapolation of this study data also indicates an approximately 18-month increase in median overall survival between patients on tafamidis versus placebo.<sup>12</sup> In addition, the pivotal data demonstrated that Vyndaqel slowed the decline in functional status and quality of life compared to placebo. That effect may be more profound for those who are diagnosed and treated early. This dual benefit—improving mortality and slowing the decline in quality of life—distinguishes the Medications from other medical therapies for chronic diseases. For example, a study of cancer medicines approved between 2009 and 2013 found that “[o]nly two of the 26 drugs shown to extend life also showed benefits on quality of life, and 33 (49%) had not shown any improvement on survival or quality of life.”<sup>13</sup>

### C. The Medications Are the Result of More than Two Decades of Research

The Medications are the result of more than two decades of research and testing. The tafamidis molecule was developed in the early 2000s using structure-based design technology. Over the next decade, extensive laboratory, pre-clinical and clinical studies evaluated both the safety and efficacy of the molecule. As with other investigational medicines for rare diseases, these studies were conducted knowing that the likelihood of success was very low.

Requestor acquired rights to the tafamidis molecule in 2010. In 2012, FDA granted Requestor an orphan drug designation for the development of tafamidis as a treatment for ATTR-CM. The next year, Requestor began enrollment in the landmark Transthyretin Amyloid Cardiomyopathy Clinical Trial (“ATTR-ACT”).

ATTR-ACT was an international, multicenter, double-blind, placebo-controlled, randomized clinical trial designed to evaluate the efficacy and safety of tafamidis in patients with ATTR-CM. The study was sponsored by Requestor and conducted by leading researchers at some of the most prominent medical institutions in the world, including Columbia University, the Mayo Clinic, Stanford University, the Cleveland Clinic, University College London and St. Bartholomew’s Hospital, London, and the French Referral Center for Cardiac Amyloidosis. The study was the largest multicenter investigation of a treatment for ATTR-CM ever conducted, enrolling 441 patients and was completed after approximately six years in February 2018.

The Medications are breakthrough medicines that change the lives of patients with ATTR-CM, who until now had no approved medicines for this rare, debilitating and fatal disease. As reported in the September 13, 2018 issue of the *New England Journal of Medicine*, the hierarchical combination of all-cause mortality and cardiovascular-related hospitalizations (the primary endpoint of the study) was significantly lower among patients who received tafamidis than among those who received placebo. At the end of the trial, 70% of tafamidis patients were alive, compared to only 57% of those receiving placebo.

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<sup>12</sup> See *supra*, footnote 2.

<sup>13</sup> See <https://www.bmjjournals.org/content/bmjj/359/bmj.j4530.full.pdf>.

Patients treated with tafamidis had a 30% lower all-cause mortality rate and experienced 32% fewer cardiovascular-related hospitalizations than those taking placebo. In addition, tafamidis treatment significantly reduced the decline in patients' functional capacity and quality of life. Given the progressive nature of the disease and the mechanism through which tafamidis reduces amyloidogenesis—by specifically stabilizing transthyretin tetramers that when misfolded can result in amyloid deposits in the heart—the drug is expected to have greater benefit when administered early in the disease course. Tafamidis was well tolerated in the trial, with a safety profile comparable to placebo and a rate of permanent discontinuation due to adverse events similar to placebo.

Based on the results of ATTR-ACT, FDA designated tafamidis a Breakthrough Therapy, a designation reserved for medications “that are intended to treat a serious condition and [for which] preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).”<sup>14</sup>

**D. Requestor Is Committed To Helping Patients Afford the Medications, But As With Other Novel Rare Disease Therapies, Gaps in Medicare Coverage May Hinder Access To The Medications For All But the Wealthiest Americans**

Requestor is committed to helping ensure that all patients suffering from ATTR-CM can afford the Medications and benefit from this breakthrough therapy. Taking into account Requestor's existing copay program for commercially insured patients, Requestor expects that the out-of-pocket cost for patients with non-Medicare insurance will be less than \$55 per month for the Medications. But if OIG prohibits Requestor from providing similar financial aid to Medicare beneficiaries, many elderly, middle-class patients suffering from ATTR-CM will be unable to afford the Medications. Under the Medicare Part D benefit structure, a patient must pay approximately \$13,000 in annual out-of-pocket expenditures for the Medications, based on mandatory coinsurance through certain Part D phases (*i.e.*, deductible, initial benefit limit, coverage gap and catastrophic) and certain formulary tiers (*e.g.*, specialty tier). This expense will present a prohibitive financial barrier for a significant proportion of elderly Medicare patients.<sup>15</sup>

Importantly, the out-of-pocket expense for the Medications is largely driven by the Medicare Part D benefit structure, not the Medications' price. Even cutting the Medications' annual list price in half would still leave many Medicare Part D patients unable to access the Medications due to the financial burden. That is because Medicare Part D beneficiaries who need high cost specialty medicines are required to pay for a large share of their medicines' costs, especially before reaching the catastrophic coverage phase of the benefit—a requirement that is particularly onerous for innovative orphan drug

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<sup>14</sup> See <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm405397.htm>.

<sup>15</sup> There is evidence that at least one quarter of new Medicare Part D prescriptions are abandoned if beneficiaries are asked to pay \$50 or more, which is often the case for specialty drugs. <https://www.finance.senate.gov/imo/media/doc/26FEB2019BOURLA-PFIZER.pdf>; IMS FIA Dataset, Amundsen Group analysis.

treatments. The Medicare Part D population is the only insured segment of the U.S. healthcare system that is not protected by a cap on annual out-of-pocket spending.<sup>16</sup>

Standard prescription drug coverage under Medicare Part D includes two distinct types of coverage: (1) defined standard coverage; and (2) actuarially equivalent standard coverage. Both types of standard coverage have similar features relevant to the cost-sharing issues we discuss in this letter.

- **Deductible and Initial Coverage Phase.** Beneficiaries who are not eligible for low-income subsidies are subject to a deductible (up to \$415 in 2019; \$435 in 2020), followed by an initial coverage phase with 25% coinsurance requirement.<sup>17</sup> Most relevant to this discussion is the ability of plans to utilize specialty tiers and non-preferred brand co-insurance tiers. The vast majority of Medicare Part D plans place drugs costing \$670 or more per month on a specialty tier, where they may be subject to up to 33% coinsurance during the initial coverage phase.
- **The “Coverage Gap.”** Once total (beneficiary plus plan) prescription drug spending hits an initial coverage limit (\$3,820 in 2019; \$4,020 in 2020), beneficiaries enter a “coverage gap,” or “donut hole” phase, during which beneficiaries pay 25% of the cost for brand-name medications, regardless of whether there is a generic alternative or whether the brand-name medication is the only available treatment option. In 2019, Manufacturers contribute a 70% discount on branded medications in the coverage gap. Part D plan liability is 5% in the coverage gap.
- **Catastrophic Coverage.** Once the beneficiaries’ True Out-of-Pocket (“TrOOP”) spending reaches a catastrophic coverage threshold (\$5,100 in 2019; \$6,350 in 2020), beneficiaries enter the catastrophic coverage phase, during which beneficiaries pay 5% of the cost of brand-name medications for the remainder of the coverage year.

Thus, many Medicare beneficiaries who need the Medications will face \$5,100 (2019) in TrOOP spending with their first prescription.<sup>18</sup> Even when they reach the catastrophic coverage phase of the benefit, the 5% coinsurance requirement will be prohibitive for many patients. The result is that many ATTR-CM patients will not be able to afford the Medicines to extend and improve their lives.

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<sup>16</sup> Jalpa A. Doshi, Pengxiang Li, and Amy R. Pettit, *Addressing Out-Of-Pocket Specialty Drug Costs in Medicare Part D: The Good, The Bad, The Ugly, And The Ignored*, HEALTH AFFAIRS BLOG, July 25, 2018, <https://www.healthaffairs.org/do/10.1377/hblog20180724.734269/full/>.

<sup>17</sup> Part D plans also may offer actuarially equivalent coverage, under which they would substitute certain cost-sharing requirements in defined standard coverage (including tiered structures tied to plan formularies or preferred pharmacies), provided that those alternative cost-sharing requirements are actuarially equivalent to the average expected coinsurance of 25% for costs above the annual deductible and up to the initial coverage limit under defined standard coverage.

<sup>18</sup> Note that the 70% manufacturer discount in the coverage gap counts towards TrOOP, thus actual out-of-pocket costs for beneficiaries who reach the catastrophic threshold is closer to \$2,750 (2019).

Cost sharing is intended to cause patients to evaluate the need for discretionary care and to consider cheaper alternatives when available, not to discourage patients from receiving necessary and potentially life-extending care when there are no other viable treatment options. But, in unique circumstances like those presented here, the Medicare Part D benefit design and patient cost-sharing obligations can deter patients from buying necessary medicines for no reason other than their inability to afford them.

Medicare Part D's Low Income Subsidy ("LIS") does not bridge the gap for most Medicare patients, because LIS provides financial relief only to patients whose incomes fall below 150% of the federal poverty line—approximately \$18,000 annually for an individual and \$38,000 annually for a family of four.<sup>19</sup> Approximately one quarter of Americans live below 150% of the federal poverty line.<sup>20</sup> The majority of Americans are considered middle class, *i.e.*, their incomes exceed 150% of the poverty line but are less than \$100,000 a year.<sup>21</sup> For those middle-class Americans, \$13,000 or more in annual cost-sharing is untenable, yet Medicare's "Low-Income Subsidy" offers them no relief. The only option for these patients is to seek financial assistance through charities or be enrolled in a manufacturer free drug program, to the extent that a manufacturer will provide free drug to insured patients.

In practical terms, the Part D cost-sharing obligations result in rationed access to outpatient prescription medications based on the patient's economic class. If a patient is relatively wealthy and able to meet the TrOOP threshold of \$5,100 in out-of-pocket expense (in 2019), then Medicare's catastrophic coverage will cover 95% of additional costs incurred for the rest of the year. But if the patient cannot afford to pay the amounts necessary to matriculate through the coverage gap, then Medicare's catastrophic coverage never kicks in and the patient accordingly does not benefit from that next stage of coverage. Perversely, that means Medicare provides substantially more financial assistance to wealthier patients than to less affluent patients, even though such less affluent patients have the same right to insurance assistance and the same medical need.<sup>22</sup>

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<sup>19</sup> While beneficiaries at 135-150% of the federal poverty line have a different level of subsidy, the same challenges apply. They pay an \$85 deductible and coinsurance of 15% up to \$5,100 (in 2019) in out-of-pocket costs, which is unattainable for many at this level of income. After that, they are eligible for copays of \$8.50 for brand name drugs.

<sup>20</sup> See <https://tinyurl.com/y7lpr9th>.

<sup>21</sup> According to U.S. Census data, 60.1% of U.S. households had annual incomes between \$15,000 and \$99,999 in 2017. Fontenot, Kayla, Jessica Semega, and Melissa Kollar, U.S. Census Bureau, Current Population Reports, pp. 60-263, *Income and Poverty in the United States: 2017*, U.S. Government Printing Office, Washington, DC, 2018. There is no public information regarding the percentage of Medicare beneficiaries that qualify for the Low-Income Subsidy.

<sup>22</sup> While Medicare Part D copay requirements help reduce government expenditure by requiring the patient to share in the expense, that interest is served equally whether the source of the copay is the patient's personal resources, a supplemental insurance policy, or a third party, such as a family member or charitable contribution. To the extent the government uses the copay requirement not to defray the government's expenditure by the amount of the copay, but to ration access to Medicare benefits to those who are able to afford the copay out of personal finances, that raises a serious constitutional question, as discussed below. See *infra* pp. 21-23.

The challenges to patient affordability as a result of Medicare's benefit design are most acute when it comes to medicines like Vyndaqel and Vyndamax that treat a rare disease and are targeted to a Medicare population. To develop these breakthrough Medications, Requestor invested substantial time and money, notwithstanding the high risk that this investment would not succeed in the development of an approved and effective therapy.<sup>23</sup> Only a small fraction of investigated therapies are ever approved.<sup>24</sup> To maintain innovation incentives and to reward entrepreneurial risk-taking, a biopharmaceutical company must be able to recoup the billions it invests in research and development during the limited time period when the company enjoys product exclusivity.<sup>25</sup> Given the additional risks and difficulties involved in developing rare-disease therapies, that financial incentive is particularly important. In addition, only a limited patient population is prescribed treatments for rare diseases. For example, only an estimated approximately 100,000 to 150,000 patients suffer from ATTR-CM, the vast majority of whom are never diagnosed or treated for the condition. In light of these factors, a biopharmaceutical company must often charge relatively high prices for such medications to justify its substantial up-front investment in their development.

These considerations, as well as their strong efficacy and safety profile and their positive impact on quality-of-life for ATTR-CM patients, justify the Medications' list price of \$225,000 for a one-year course of treatment. In fact, the Medications' price is lower than the average annual list price (\$300,000) of the 34 rare-disease medicines that FDA approved in 2018,<sup>26</sup> and is approximately half the \$450,000 list price for Onpattro®

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<sup>23</sup> Substantial research and development time and costs are required to develop novel therapies like the Medications. Today, it takes about 10 years for a medicine to make its way from initial discovery through FDA approval, at an average cost of \$2.6 billion (2015 data). See <https://www.phrma.org/report/biopharmaceutical-research-and-development-the-process-behind-new-medicines>. The development of medicines for rare diseases is complicated by the fact that the diseases typically are not well-characterized or understood, appropriate efficacy endpoints are not defined, and patient populations are very small. These unique challenges make development of medicines for rare diseases even more difficult and expensive. As a consequence of these hurdles, the costs of developing medicines for rare (and other) diseases has continued to rise. As the Office of Health Economics ("OHE") observed in 2012, since the 1970s, biopharmaceutical companies' out-of-pocket drug development expenditures have risen by 600%, success rates have fallen by 50%, research and development time has increased by more than seven years, and the cost of capital has risen by 3%. See <https://www.ohe.org/news/overview-ohe-study-cost-drug-development-presented>.

<sup>24</sup> It is estimated that nine out of every ten investigational medicines never are approved for human use. See <https://www.ohe.org/news/overview-ohe-study-cost-drug-development-presented>.

<sup>25</sup> After a manufacturer's exclusivity period ends, the medicine effectively becomes societal property, freely available to others, including generic pharmaceutical companies which can sell the medicine without bearing any of the costs associated with bringing it to market. These innovative medicines also serve as predicates for new drug development. Future therapies and innovation in the relevant disease states often are brought to market by other companies who benefit from the groundbreaking work done prior to original market approval.

<sup>26</sup> Based on published list price for standard one-year course. Excludes TPOXX (ivosidenib) and Asparlas (calaspargase pegol-mknl) for which pricing is not available.

(patisiran) and Tegsedi™ (inotersen)—two recently approved therapies for amyloid transthyretin polyneuropathy (“ATTR-PN”), a condition similar to ATTR-CM.<sup>27</sup>

### III. PROPOSED COPAY ASSISTANCE PROGRAM

Requestor seeks OIG approval to offer copay assistance to eligible Medicare Part D beneficiaries to help them pay the TrOOP costs required to reach the catastrophic phase of their Part D benefit, and to pay the 5% coinsurance required in the catastrophic phase. Requestor’s goal is to help ensure that, once the Medications have been appropriately prescribed, all ATTR-CM patients can access them. Requestor thus proposes two possible solutions to facilitate ATTR-CM patients’ access to the Medications.

Requestor proposes a Copay Assistance Program to provide copay assistance directly to eligible Medicare Part D beneficiaries to help them pay the TrOOP costs required to matriculate through the Part D deductible, initial coverage phase and coverage gap and then to assist patients with affording the 5% coinsurance required during the catastrophic phase. To be eligible to receive copay assistance under this program, patients must: (1) be prescribed the Medications for an on-label indication; (2) be U.S. residents; and (3) meet program criteria for financial need. These amounts should count toward the beneficiary’s TrOOP, so that the patient can reach catastrophic coverage.<sup>28</sup> To receive assistance from the Copay Assistance Program, Eligible Part D beneficiaries would be required to enroll in the program and pay a copay of up to \$35 per month, after which Requestor would pay 100% of each enrolled Medicare Part D beneficiary’s monthly deductible or coinsurance amounts for the Medications.

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<sup>27</sup> ATTR-PN is a related condition caused by deposition of amyloid fibrils in nerves and other parts of the body. The symptoms typically are neurologic in nature, including carpal tunnel syndrome, autonomic dysfunction, unexplained weight loss, and polyneuropathy. Progressive organ dysfunction and death typically occurs within 10 years of disease onset. The global prevalence of ATTR-PN is estimated at 10,000 people.

<sup>28</sup> CMS regulations and guidance and OIG guidance support including these amounts in a patient’s TrOOP. The regulation regarding TrOOP (42 C.F.R. § 423.464(f)(2) states that the Part D plan must include the beneficiary’s “incurred costs” (as defined in 42 C.F.R. § 423.100), which includes costs incurred by a Part D enrollee that are paid for by the enrollee or on behalf of the Part D enrollee by another person. The term “person” is defined broadly to include corporations. In the preamble to its 2005 Medicare Part D final rule, in response to a question about the scope of the term “person,” CMS explained that: “regardless of whether a manufacturer patient assistance program is a bona fide charity for the purpose of Federal fraud and abuse laws, any drug payments it makes on behalf of Part D enrollees would count toward TrOOP unless these organizations qualify as group health plans, insurance or otherwise, or similar third-party payment arrangements.” 70 Fed. Reg., No 18, 4194, 4239 (Jan. 28, 2005).

Similarly, in OIG’s Special Advisory Bulletin on Patient Assistance Programs for Medicare Part D Enrollees, OIG acknowledged that that “beneficiaries may count toward their TrOOP any assistance received from any source other than group health plans, other insurers and government funded health programs, and similar third-party payment arrangements. The preamble to the Part D regulations explains that cost-sharing assistance furnished by a PAP, including a manufacturer PAP, will count toward a beneficiary’s TrOOP expenditures, even if the PAP does not comply with the fraud and abuse laws. This approach relieves beneficiaries of the financial risk of accepting assistance from an entity that may be improperly structured or operated.” 70 Fed. Reg., No. 224, 70623, 70625 (Nov. 22, 2005).

Requestor would not offer its Copay Assistance Program as part of any advertisement or solicitation for the Medications. Nor would Requestor routinely provide copay assistance to all patients prescribed the Medications. Rather, Requestor would conduct an individualized, case-by-case income determination, based on a uniform measure of financial need, to ensure that patients meet the program requirements. Requestor would substantiate those financial need determinations through appropriate documentation.

#### IV. QUESTIONS PRESENTED

The questions presented are:

1. Does the proposed arrangement implicate the AKS, SSA §§ 1128B(b), by providing prohibited remuneration within the meaning of that statute?
2. Does the proposed arrangement implicate the BIS, SSA § 1128B(a)(5), by providing prohibited remuneration within the meaning of that statute?
3. Even if OIG believes that the proposed arrangement implicates the AKS or the BIS by providing *potentially* prohibited remuneration, would OIG provide a safe harbor on the basis that the arrangement raises no more than a low risk of fraud and abuse under OIG's prudential factors?

#### V. LEGAL ANALYSIS

As described below, under the circumstances presented, Requestor's proposed Copay Assistance Program does not implicate either the AKS or the BIS. The program meets the statutory criteria under the AKS and the BIS that expressly permit copay waivers as an exception to the definition of otherwise prohibited "remuneration." Even apart from the statutory exception, copay assistance that allows Medicare beneficiaries to access this breakthrough therapy would not amount to inducement to prescribe the Medications. Rather, physicians will prescribe the Medications and patients will fill those prescriptions because the Medications are a safe and highly effective treatment for ATTR-CM that extends patients' lives, slows the decline in functional status and quality of life, and reduces cardiovascular-related hospitalizations.

Even if the proposed arrangement did implicate the AKS or the BIS, the unique factors presented here warrant the exercise of OIG's enforcement discretion under the prudential factors. The Copay Assistance Program meets each of those factors. Specifically, the proposed arrangement: (1) supports, rather than interferes with, clinical decision-making by encouraging prescription of the Medications on the basis of medical need rather than a patient's ability to pay; (2) potentially avoids unnecessary hospitalizations and potentially saves overall medical system costs; (3) encourages appropriate utilization of Medicare Part D, not overutilization, (4) improves patient safety

and quality of care by promoting access to a life-extending and safe therapy; (5) expands patients' freedom of choice; and (6) does not result in unfair competition.

The exercise of enforcement discretion is further warranted to avoid serious constitutional concerns under the Equal Protection Clause. Prohibiting the proposed Copay Assistance Program would irrationally deny Medicare beneficiaries access to these critical, life-extending Medications solely on the basis of socio-economic status. A rule that irrationally discriminates against Medicare patients on the basis of financial status would run afoul of the Equal Protection Clause.

The proposed Copay Assistance Program would enable all ATTR-CM patients, including federal healthcare beneficiaries, to access the Medications. Because of the unique facts presented by the disease and this treatment, such financial assistance would pose no risk of fraud, abuse, overutilization, or improper interference with clinical decision-making. Accordingly, OIG approval of the proposed arrangement will advance the core purpose of Medicare Part D, which is to make effective prescription drugs available to all eligible Medicare recipients.

#### **A. The Copay Assistance Program Does Not Implicate the AKS or the BIS**

1. *The Proposed Copay Assistance Program Does Not Constitute Prohibited "Remuneration," Because it Falls into the Statutory Exception Permitting Copay Waivers.*

The AKS and the BIS prohibit offering or paying "remuneration" to a person to induce or influence the purchase of goods paid for by federal health programs.<sup>29</sup> The proposed Copay Assistance Program falls within the statutory and regulatory exception to prohibited "remuneration" that permits coinsurance and deductible waivers. In particular, the BIS expressly excludes waivers of coinsurance or deductibles from the statutory definition of "remuneration" if—

- (i) the waiver is not offered as part of any advertisement or solicitation;
- (ii) the person does not routinely waive coinsurance or deductible amounts; and
- (iii) the person—

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<sup>29</sup> Specifically, the AKS prohibits offering or paying "remuneration" "to any person to induce such person to purchase ... any good ... for which payment may be made in whole or in part under a Federal health care program." 42 U.S.C. § 1320a-7b(b)(2)(B). Similarly, the BIS prohibits "offer[ing] to or transfer[ing] remuneration to any individual eligible for [Medicare, Medicaid or certain other federally funded State health care programs] ... that such person knows or should know is likely to influence such individual to order or receive from a particular provider, practitioner, or supplier any item or service for which payment may be made, in whole or in part," under federal health care programs. 42 U.S.C. § 1320a-7a(a)(5).

(I) waives the coinsurance and deductible amounts after determining in good faith that the individual is in financial need; or

(II) fails to collect coinsurance or deductible amounts after making reasonable collection efforts;

42 U.S.C. § 1320a-7a(i)(6)(A). The regulatory definition of “remuneration” under the AKS similarly excepts copay waivers. *See* 42 C.F.R. § 1003.110. As HHS has explained, the copay waiver safe harbor is an “important exception” that allows “suppliers … [to] forgive the copayment in consideration of a particular patient’s financial hardship.” *See Publication of OIG Special Fraud Alerts*, 59 Fed. Reg. 65,372, 65,375 (Dec. 19, 1994).

The proposed Copay Assistance Program meets each of the three prongs of the copay waiver exception. Requestor would provide financial assistance to eligible patients by waiving copays and assisting with the payment of Medicare Part D coinsurance and deductibles. Requestor would not offer financial assistance as part of any advertisement to solicit prescriptions for the Medications.<sup>30</sup> Rather, Requestor would offer copay and coinsurance assistance only to patients properly diagnosed with ATTR-CM who have already been prescribed the Medications by their physician. The waivers also would not be “routine,” and would instead be granted on a case-by-case basis upon a documented demonstration of financial need based on patient income levels.

OIG has approved other copay assistance programs similar to those Requestor now proposes when offered by hospitals and direct service providers. In those cases, OIG has reasoned that, because the proposed programs included appropriate safeguards, they satisfied the copay waiver exception to “remuneration” and therefore did not implicate the AKS or the BIS. *See* Advisory Opinion No. 17-02, at 6-7 (July 7, 2017). OIG has similarly approved a need-based copay waiver program for a corporation that provided emergency-only ambulance services. *See* Advisory Opinion No. 12-16, at 4-5 (Nov. 5, 2012).

But OIG has deviated from the statutory text and its treatment of providers’ copay waiver programs by concluding that pharmaceutical manufacturers are, at least generally, ineligible to take advantage of the copay waiver exception to the AKS or the BIS. *See* Advisory Opinion No. 03-3, at 5-6 (Feb. 12, 2003); *see also* OIG Special Advisory Bulletin on Patient Assistance Programs for Medicare Part D Enrollees, 70 Fed. Reg. 70623, 70626 (Nov. 22, 2005). That carve-out for only manufacturers is not supported by the statutory or regulatory text that expressly permits copay assistance waivers without any manufacturer exception. Thus, regardless of any policy arguments that OIG may feel would support excluding manufacturers from the copay waiver exception, OIG has no legal authority to effect that exclusion.

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<sup>30</sup> To be sure, Requestor would provide information to patients prescribed the Medications, such as through a consumer-facing website and a patient support hub, about where and how to access copay assistance, in order to connect patients with the assistance. Such communications, directed to patients after they have been diagnosed as having the condition, does not constitute the type of “advertising” that the BIS discourages, which is directed at communications that could influence the doctor’s prescribing decision.

Even if OIG were authorized to fashion an exclusion for manufacturers—which it is not—OIG’s policy reasons for a manufacturer carve-out are inapplicable here. OIG’s policy reasons for that manufacturer carve-out are also inapplicable here. OIG has asserted that copay assistance provided by pharmaceutical manufacturers “differ[s] in two important respects” from that provided by hospitals and pharmacies (1) by creating “an economic incentive [for suppliers] to favor” products eligible for copay assistance and (2) because “the availability of [such] … assistance is typically advertised and may influence a beneficiary’s choice of product (through the prescribing physician acting on behalf of the beneficiary).” *Id.* OIG has also expressed concern that beneficiaries who receive copay assistance may be “effectively locked into using the pharmaceutical manufacturer’s product, since the beneficiary risks losing financial assistance if he or she switches products, even if an equally effective, but less expensive, product would be in his or her best medical interests.” *Id.* HHS’s 2014 Special Advisory Bulletin on copayment coupons similarly contended that manufacturers’ copay assistance programs can make patients price-insensitive and discourage price competition between pharmaceutical companies. *See Special Advisory Bulletin on Pharmaceutical Manufacturer Copayment Coupons*, at 2 (Sept. 2014).

But OIG’s concerns about improper incentives and influence are not applicable to Requestor’s proposed Copay Assistance Program. Physicians receive no incentive to “favor” the Medications. They will make prescribing decisions based on clinical diagnosis and the Medications’ efficacy and safety for treating ATTR-CM. Similarly, in the absence of alternative therapies, copay assistance will not “lock” patients out of switch opportunities. OIG accordingly should follow the plain text of the BIS statute and the AKS regulations to permit the proposed Copay Assistance Program. OIG should further construe the BIS and the AKS in a manner that advances Medicare’s mission to enable low-income elderly patients to access healthcare and avoids the equal protection concerns highlighted below.

*2. Copay Assistance For the Medications Neither “Induces” nor “Influences” the Selection of the Medications as an ATTR-CM Treatment*

Even apart from the statutory exception, the financial assistance provided through the proposed Copay Assistance Program would not improperly “induce” or “influence” physicians to prescribe or patients to use the Medications. The AKS prohibits offering or paying “remuneration” “to any person *to induce* such person to purchase … any good … for which payment may be made in whole or in part under a Federal health care program.” 42 U.S.C. § 1320a-7b(b)(2)(B) (emphasis added). Similarly, the BIS prohibits “offer[ing] to or transfer[ing] remuneration to any individual eligible for [Medicare, Medicaid or certain other federally funded State health care programs] … that such person knows or should know is likely *to influence* such individual to order or receive from a particular provider, practitioner, or supplier any item or service for which payment may be made, in whole or in part,” under federal health care programs. 42 U.S.C. § 1320a-7a(a)(5) (emphasis added).

ATTR-CM is a rare, progressive, fatal disease. Diagnosis of ATTR-CM is not subjective. Instead, ATTR-CM is diagnosed based on specific medical tests including heart biopsy and nuclear scintigraphy. Thus, prescriptions for these orphan medicines will be written only for the limited population of patients who have been objectively diagnosed as suffering from ATTR-CM. Moreover, the proposed program will limit copay relief to appropriate, financially-needy patients and will not “induce” or “influence” a physician to prescribe the Medications or a patient to purchase the Medications rather than an alternative, possibly more economical, treatment. Further, any offer of copay assistance will occur only *after* a physician diagnoses a patient with ATTR-CM and prescribes the Medications. Physicians will prescribe the Medications to treat ATTR-CM because the Medications are highly effective and have a favorable safety profile.

Under these circumstances, the Copay Assistance Program will facilitate a patient’s access to the Medications, not improperly induce or influence their use. Requestor’s proposed program thus removes barriers to treatment and facilitates adherence to independent treatment decisions that have been made based on sound medical judgment and scientific evidence. The program would not taint physicians’ decisions; rather, it would enable patients to overcome otherwise insurmountable financial obstacles to obtaining a medically necessary therapy. The program is thus consistent with the intent of the AKS and the BIS, which protect against “potential harm...that [an HCP’s] judgment will not be based solely on legitimate considerations such as cost, quality, and the need for the services, but will at least in part be based on [an] expectation that he will receive the kickback.” *Inspector Gen. v. The Hanlester Net.*, DAB 1275, at 12 (H.H.S. Sept. 18, 1991); *United States v. Patel*, 778 F.3d 607, 612 (7th Cir. 2015) (AKS was enacted to “protect the Medicare and Medicaid programs from increased costs and abusive practices resulting from provider decisions that are based on self-interest rather than cost, quality of care or necessity of services”).

**B. Even if the Copay Assistance Program Implicates the AKS or the BIS, Enforcement Discretion Is Warranted Under OIG’s Prudential Factors.**

Even if OIG believes that the Copay Assistance Program implicates the AKS or the BIS, there could hardly be a stronger case for the exercise of enforcement discretion than this one. Application of OIG’s prudential factors shows that the program presents low risk of fraud and abuse.

Many common practices that do not fall within a statutory or regulatory safe harbor are not necessarily illegal under the AKS or the BIS. Consequently, OIG’s enforcement efforts are focused on potentially “fraudulent or abusive” practices that could create risks to federal health care programs or their beneficiaries. Thus, in assessing the potential risk for fraud or abuse, OIG appears most concerned with arrangements that have a potential to:

- (1) interfere with clinical decision-making;
- (2) increase costs to federal health care programs;

- (3) increase the risk of overutilization or inappropriate utilization;
- (4) raise patient safety or quality of care concerns;
- (5) limit patient freedom of choice; and
- (6) result in unfair competition.

*See* 68 Fed. Reg. at 23734; *see also, e.g.*, OIG Adv. Op. No. 98-07, at 5 (June 11, 1998). These factors are sometimes referred to as the “prudential factors” or the “OIG enforcement considerations.” In any advisory opinion, OIG carefully evaluates these factors, and that analysis typically is determinative of OIG’s conclusions as to whether to recognize a safe harbor concerning specific conduct.

The proposed Copay Assistance Program is supported by each of the prudential factors. The Medications are the only FDA-approved treatment for ATTR-CM and have demonstrated efficacy and safety for patients with this complex and deadly disease. The Medications offer strong clinical value for these patients who have no other treatment option. Copay assistance that enhances access to the Medications for patients otherwise unable to afford them promotes all of the Medicare Part D program goals without any of the accompanying risks of fraud or abuse that might arise in the context of other therapies. As a result, the proposed arrangement: (1) supports, rather than interferes with, clinical decision-making by encouraging prescription of the Medications on the basis of medical need rather than a patient’s ability to pay; (2) potentially avoids unnecessary hospitalizations and potentially saves overall medical system costs; (3) encourages appropriate utilization of Medicare Part D, not overutilization; (4) improves patient safety and quality of care by promoting access to a life-extending and safe therapy; (5) expands patients’ freedom of choice; and (6) does not result in unfair competition.

Requestor should be permitted to help patients covered by Medicare who are diagnosed with ATTR-CM and prescribed the Medications to gain access to treatment that they otherwise may not be able to afford. Copay support in this context is designed to allow doctors to make treatment decisions in the best clinical interest of the patient and to help ensure that financial need does not impede patient access to the Medications. Without copay support, only patients with commercial insurance and those with substantial financial means will be able to access the sole effective treatment for this condition. That perverse result would not advance Medicare’s purpose.

Additionally, approving Requestor’s proposed Copay Assistance Program would allow OIG to avoid a significant constitutional question. Serious equal protection concerns are raised by a prohibition of a program that results in circumstances that irrationally ration patients’ access to the Medications solely on the basis of their socio-economic status. OIG can avoid this significant issue by appropriately interpreting the AKS and the BIS not to bar Requestor’s proposed arrangement.

*1. The Program Does Not Interfere with Clinical Decision-Making*

Requestor's proposed Copay Assistance Program would not interfere with clinical decision-making. The Medications are a "breakthrough therapy," the only FDA-approved medicines for treatment of ATTR-CM, and the only treatment proven to reduce mortality and slow decline in quality of life for patients with this deadly disease. The Medications thus offer a significant therapeutic benefit with minimal safety risks. The only potential alternative treatment is dual heart and liver transplant, which is: (1) of limited utility as most patients with ATTR-CM are too sick and have too many other medical problems to meet transplant criteria; and (2) far more expensive than the Medications. Copay assistance would be offered only after a patient was properly diagnosed with ATTR-CM and after a physician decided to prescribe the Medications. Under these circumstances, copay assistance would not improperly alter clinical decision-making. Requestor's proposed program is designed only to help ensure that patients who are properly prescribed the Medications for an on-label use have access to the Medications regardless of their ability to pay. These factors distinguish the proposed program from copay programs involving other medications and disease states that have been prohibited under prior OIG guidance.

*2. The Program Does Not Increase Federal Program Costs and Likely Would Save the Federal Government Money*

The Copay Assistance Program would not inappropriately increase costs to federal healthcare programs, and more likely would produce cost savings. Prescriptions for the Medications will be written only for the limited population of patients who have been objectively diagnosed with ATTR-CM. Moreover, the Medications are far less expensive than a dual heart and liver transplant, the only disease-altering treatment currently available to patients with ATTR-CM. The Medications also may lower other healthcare costs associated with ATTR-CM. In the pivotal clinical trial, patients treated with the Medications experienced 32% fewer cardiovascular-related hospitalizations than those taking placebo. In any event, any additional expenditure required for the Medications would be appropriate and necessary to allow patients to benefit from a life-extending, breakthrough treatment for a debilitating and fatal condition, as evidenced by Medicare's willingness to pay its share of the Medications' cost for beneficiaries who are able to afford their coinsurance obligations from their personal resources.

*3. The Program Promotes Appropriate Utilization, Not Overutilization*

The Copay Assistance Program would not cause overutilization or inappropriate utilization of the Medications. As discussed above, the Medications are the only FDA-approved medicines for ATTR-CM, and only patients diagnosed with ATTR-CM who are prescribed the Medications on-label<sup>31</sup> by their physician and who have demonstrated financial need will be eligible for copay assistance. Thus, the effect of the proposed

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<sup>31</sup> Requestor's sales and medical affairs personnel at all times will describe the clinical evidence supporting use of the Medications in an accurate, complete and non-misleading manner.

program would not be to induce unwarranted prescriptions, but to help ensure that appropriate patients have access to therapy regardless of their ability to pay.

*4. The Program Promotes Patient Safety and Quality of Care*

For the same reasons that copay assistance for the Medications would promote appropriate utilization, it also would promote patient safety and quality of care. For most patients with ATTR-CM, the Medications will be the best and only treatment available to them. The fact that the Copay Assistance Program would increase access to the Medications for appropriate patients would improve the quality of patient care and patient outcomes.

*5. The Program Expands Patient Freedom of Choice*

Copay assistance would make it possible for all eligible patients to use the Medications without regards to ability to pay. The Copay Assistance Program thus would expand patient freedom of choice. The lack of alternatives to the Medications eliminates the concern, cited in prior OIG advisory opinions, that patients could be locked into a particular product because of financial incentives.

*6. The Program Has No Adverse Impact on Competition*

Because there are no other FDA-approved treatments for ATTR-CM, copay assistance for the Medications would have no adverse impact on competition.

**C. Providing a Safe Harbor for Requestor's Copay Assistance Program Avoids A Significant Constitutional Question**

Granting a safe harbor for Requestor's Copay Assistance Program would allow OIG to avoid a significant constitutional question. Interpretation of the AKS and the BIS that irrationally precludes access to life-saving medicine for poorer patients while covering costs for wealthier patients raises serious equal protection concerns.

The Fifth Amendment's Due Process Clause entitles every person to the equal protection of the laws. *See United States v. Windsor*, 133 S. Ct. 2675, 2695 (2013). Classifications based on income, wealth, and age are all subject to rational basis scrutiny. *See Harris v. McRae*, 448 U.S. 297, 326 (1980); *Maher v. Roe*, 432 U.S. 464, 470-471 (1977); *Mass. Bd. Of Retirement v. Murgia*, 427 U.S. 307, 312 (1976). Under rational basis scrutiny, a statute is "accorded a strong presumption of validity" and will be upheld if "any reasonably conceivable state of facts" could demonstrate that the statute is "rationally related to a legitimate government purpose." *Heller v. Doe*, 509 U.S. 312, 319-20 (1993). But laws can, and do, fail rational basis scrutiny when, for example, it "would have been irrational for Congress to" draw the distinctions in a statute to achieve its purposes. *Shelby Cty., Ala. v. Holder*, 570 U.S. 529, 556 (2013).

In particular, laws that discriminate on the basis of poverty have a measure of special constitutional significance. *See McDonald v. Board of Election Comm'r of Chicago*, 394 U.S. 802, 807 (1969) (careful examination is especially warranted where lines are drawn on the basis of wealth); *Harper v. Virginia Bd. of Elections*, 383 U.S. 663, 668 (1966) (lines drawn on the basis of wealth are traditionally disfavored). As such, the Court has repeatedly invalidated statutes, on their face or as applied, that discriminated against the poor. *See Little v. Streater*, 452 U.S. 1 (1981); *Bullock v. Carter*, 405 U.S. 134, 144 (1972); *Harper*, 383 U.S. at 668; *Griffin v. Illinois*, 351 U.S. 12, 17, n.11 (1956).

In these unique circumstances, rationing Medicare Part D beneficiaries' access to the Medications by prohibiting them from benefitting from Requestor's proposed Copay Assistance Program would result in irrational discrimination against middle-class Americans. In the absence of copay assistance, two patients—each with the same medically certain diagnosis, each of whom will benefit equally from the Medications—would have significantly different experiences. Under the OIG's guidance, the patient who is able to cover the approximately \$13,000 in out-of-pocket costs during the year will be able to benefit from the Part D program covering the remaining amount (over \$200,000) and enjoy the clinical benefits of therapy. The patient who cannot afford the approximately \$13,000 in out-of-pocket costs without assistance from Requestor cannot take advantage of their Part D coverage and the clinical benefits of therapy. Even assuming such a distinction would survive equal protection scrutiny where there is a genuine concern of fraud or abuse due to the potential source of copayments, the distinction is irrational where, as here, no such risk exists.

A decision to prohibit the proposed program would deny access to the Medications *only* for non-Low Income Subsidy Medicare Part D enrollees who lack independent financial recourse. Uninsured and commercially insured patients typically have options available to defray high drug costs. Medicaid patients have significantly lower copay obligations. Medicare beneficiaries with means to pay their TrOOP costs can afford to cover their costs for the Medications (and any other prescribed medications) and reach the catastrophic coverage phase, in which 95% of the Medications' costs will be covered. Meanwhile, without the support of direct financial assistance, Medicare beneficiaries who lack independent resources are unfairly and seriously disadvantaged and are denied insurance coverage for this lifesaving treatment.

Congress could not rationally establish a public health insurance program that provides greater benefits to individuals the *wealthier* they are. That would get the scheme entirely backwards. That is why Congress created an express statutory exception to the AKS and the BIS for copay waivers and for arrangements that "promote access to care." The whole purpose of a public insurance program is to make it so that rich and poor alike have access to medical care. The additional fact that the public insurance scheme disproportionately prevents older patients (who are more likely to be diagnosed with ATTR-CM) from obtaining access to the Medications when younger patients with commercial insurance may easily do so compounds the constitutional concerns.

If OIG interprets the statute to prevent copay assistance to those who are unable to pay, where there is minimal risk of fraud or abuse, that interpretation would raise serious questions about whether the statute is fundamentally irrational and unconstitutional under the equal protection principles enshrined in the Fifth Amendment's Due Process Clause. Indeed, OIG recognized as much in its 2016 regulations implementing the "promotes access to care" safe harbor to the BIS, where OIG defended its proposed expansion of protections for arrangements that promote access to care by saying: "We recognize that there are socioeconomic, educational, geographic, mobility, or other barriers that could prevent patients from getting necessary care (including preventive care) or from following through with a treatment plan. Our interpretation of items or services that "promote access to care" encompasses giving patients the tools they need to remove those barriers.<sup>32</sup> Requestor's Copay Assistance Program likewise "removes those barriers" and therefore should be subject to a safe harbor.

## VI. CONCLUSION

Requestor is committed to ensuring that the important clinical benefits of the Medications are available to ATTR-CM patients regardless of their ability to pay, while also complying fully with the AKS and the BIS. To those ends, Requestor proposes a program of copay assistance that would not provide prohibited "remuneration" to patients or providers, and would not "induce" or "influence" prescribing decisions relating to the Medications. Under the program, Requestor would provide copay assistance in carefully circumscribed circumstances and according to strict limitations, including:

- Requestor would provide copay assistance as a "waiver of coinsurance and deductible amounts"; such assistance would not be "offered as part of any advertisement or solicitation"; the assistance would not be offered routinely; and the assistance would be provided only after a good faith determination of financial need; and thus, under the statutory exclusion, such assistance would not constitute "remuneration";
- Requestor would provide copay assistance only to patients who have been prescribed the Medications by a physician, based on independent medical judgment and following objective diagnosis of ATTR-CM; and neither prescribers nor patients would receive any benefits that would induce or influence prescribing decisions, or affect medical judgment; and
- Requestor would not provide copay assistance for treatment of any disease other than ATTR-CM.

For the reasons discussed above, Requestor respectfully seeks an advisory opinion that the proposed arrangement would not constitute:

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<sup>32</sup> 81 Fed Reg. 88368, 88393 (Dec. 7, 2016).

- prohibited remuneration or inducement within the meaning of the AKS and the BIS;
- grounds for the imposition of sanctions under the BIS; or
- a basis to impose sanctions under SSA §§ 1128(b)(7) or 1128A(a)(7) as they relate to the AKS.

If OIG believes that the proposed Copay Assistance Program would provide prohibited remuneration implicating the above-cited provisions, Requestor respectfully requests that OIG issue an advisory opinion establishing a safe harbor for the program. Given the progressive and deadly nature of ATTR-CM, and because the Medications are the only available medical treatment options for patients with ATTR-CM, Requestor respectfully reiterates its request that OIG provide a response to this request within 60 days of this submission. Requestor seeks to collaboratively find a means of ensuring access to the Medications for qualifying patients.

Respectfully submitted,

  
Jeffrey L. Handwerker

**Exhibit A**

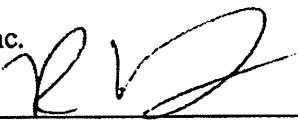
**Signed Certification by Requestor**

The arrangement described in this request for an advisory opinion is one that Pfizer Inc. in good faith plans to undertake.

With knowledge of the penalties for false statements provided by 18 U.S.C. § 1001 and with knowledge that this request for an advisory opinion is being submitted to the Department of Health and Human Services, I certify that all of the information provided is true and correct, and constitutes a complete description of the facts regarding which an advisory opinion is sought, to the best of my knowledge and belief.

Dated: August 21, 2019

Pfizer Inc.

  
Richard Nolan Townsend  
North America Regional President, Rare  
Disease Business Unit

**Exhibit B**

**Declaration Regarding No Request for Opinion from CMS**

Pfizer Inc. has not sought and will not seek an advisory opinion from the Centers for Medicare and Medicaid Services (“CMS”) on whether the arrangement implicates the Stark Act, 42 U.S.C. § 1395nn, or the Stark Regulations, 42 C.F.R. § 411.350 *et seq.*

**Exhibit C**

**Entities Controlled or Owned by Pfizer Inc.**

**Pfizer Inc. Subsidiaries**

- Agouron Pharmaceuticals, LLC
- AH Robins LLC
- AHP Holdings B.V.
- AHP Manufacturing B.V.
- Alpharma Holdings LLC
- Alpharma Pharmaceuticals LLC
- Alpharma Specialty Pharma LLC
- Alpharma USHP LLC
- American Food Industries LLC
- Anacor Pharmaceuticals, Inc.
- Array BioPharma Inc.
- Array BioPharma Limited
- Ayerst-Wyeth Pharmaceuticals LLC
- Bamboo Therapeutics, Inc.
- BINESA 2002, S.L.
- Bioren, LLC
- Blue Whale Re Ltd.
- C.P. Pharmaceuticals International C.V.
- CICL Corporation
- COC I Corporation
- Coley Pharmaceutical GmbH
- Coley Pharmaceutical Group, Inc.
- Continental Pharma, Inc.
- Cyanamid de Argentina S.A.
- Cyanamid de Colombia, S.A.
- Cyanamid of Great Britain Limited
- Distribuidora Mercantil Centro Americana, S.A.
- Encysive Pharmaceuticals Inc.
- Esperion LUV Development, Inc.
- Excaliard Pharmaceuticals, Inc.
- Farminova Produtos Farmaceuticos de Inovacao, Lda.
- Farmogene Productos Farmaceuticos Lda
- FoldRx Pharmaceuticals, Inc.
- Fort Dodge Dominicana, S.A.
- Fort Dodge Manufatura Ltda.
- G. D. Searle & Co. Limited
- G. D. Searle International Capital LLC
- G. D. Searle LLC

- Genetics Institute, LLC
- GenTrac, Inc.
- GI Europe, Inc.
- GI Japan, Inc.
- Greenstone LLC
- Haptogen Limited
- HBAF Ltd.
- Hospira (China) Enterprise Management Co. Ltd.
- Hospira Adelaide Pty Ltd
- Hospira Aseptic Services Limited
- Hospira Australia Pty Ltd
- Hospira Bahamas (Ireland) Corp.
- Hospira Bahamas Biologics Ltd.
- Hospira Benelux BVBA
- Hospira Enterprises B.V.
- Hospira France SAS
- Hospira Holdings (S.A.) Pty Ltd
- Hospira Invicta, S.A.
- Hospira Ireland Holdings Unlimited Company
- Hospira Ireland Sales Limited
- Hospira Limited
- Hospira Malaysia Sdn Bhd
- Hospira Nordic AB
- Hospira NZ Limited
- Hospira Philippines, Inc.
- Hospira Pte. Ltd.
- Hospira Pty Limited
- Hospira Puerto Rico, LLC
- Hospira Singapore Pte Ltd
- Hospira UK Limited
- Hospira Worldwide, LLC
- Hospira Zagreb d.o.o.
- Hospira, Inc.
- Industrial Santa Agape, S.A.
- InnoPharma Licensing, LLC
- InnoPharma, Inc.
- Innovative Drug Delivery Systems, Inc.
- International Affiliated Corporation LLC
- IP Pharmaceuticals India Private Limited
- Javelin Pharmaceuticals, Inc.
- JMI-Daniels Pharmaceuticals, Inc.
- John Wyeth & Brother Limited
- Kiinteistö oy Espoon Pellavaniementie 14

- King Pharmaceuticals Holdings LLC
- King Pharmaceuticals LLC
- King Pharmaceuticals Research and Development, LLC
- Korea Pharma Holding Company Limited
- Laboratoires Pfizer, S.A.
- Laboratorios Parke Davis, S.L.
- Laboratorios Pfizer Ltda.
- Laboratórios Pfizer, Lda.
- Laboratorios Wyeth LLC
- Laboratorios Wyeth S.A.
- Mayne Pharma IP Holdings (Euro) Pty Ltd
- Medivation Field Solutions LLC
- Medivation LLC
- Medivation Neurology LLC
- Medivation Prostate Therapeutics LLC
- Medivation Services LLC
- Medivation Technologies LLC
- Meridian Medical Technologies Limited
- Meridian Medical Technologies, Inc.
- Monarch Pharmaceuticals, LLC
- MPP Trustee Limited
- MTG Divestitures LLC
- Neusentis Limited
- PAH USA IN8 LLC
- Parke Davis Limited
- Parke Davis Productos Farmaceuticos Lda
- Parke, Davis & Company LLC
- Parkedale Pharmaceuticals, Inc.
- Parke-Davis Manufacturing Corp.
- PBG Puerto Rico LLC
- PCH SpinCo B.V.
- P-D Co., LLC
- Peak Enterprises LLC
- PEMB OFG Spain Holding, S.L.
- PF Asia Manufacturing B.V.
- PF Consumer Healthcare Austria GmbH
- PF Consumer Healthcare Holdings LLC
- PF Consumer Healthcare Holdings US Inc.
- PF Consumer Healthcare Ireland Unlimited Company
- PF Consumer Healthcare Korea Limited
- PF Consumer Healthcare Panama S. de R.L.
- PF Czech Republic Holdings B.V.
- PF Finland Holdings B.V.

- PF OFG Australia Pty Ltd
- PF OFG Ireland 1 B.V.
- PF OFG Ireland 2 B.V.
- PF OFG Mexico B.V.
- PF OFG Mexico, S. de R.L. de C.V
- PF OFG New Zealand ULC
- PF OFG Philippines B.V.
- PF OFG Philippines, Inc.
- PF OFG Sdn. Bhd.
- PF OFG South Korea 1 B.V.
- PF OFG South Korea 2 B.V.
- PF OFG Spain B.V.
- PF PEM FZ-LLC
- PF PR Holdings C.V.
- PF PRISM C.V.
- PF PRISM Holdings B.V.
- PF PRISM Holdings S.a.r.l.
- PF PRISM IMB B.V.
- PF Prism S.á.r.l.
- PFE Holdings G.K.
- PFE Pfizer Holdings 1 LLC
- PFE PHAC Holdings 1 LLC
- PFE Wyeth Holdings LLC
- PFE Wyeth-Ayerst (Asia) LLC
- Pfizer
- Pfizer (China) Research and Development Co. Ltd.
- Pfizer (Malaysia) Sdn Bhd
- Pfizer (Perth) Pty Ltd
- Pfizer (Thailand) Limited
- Pfizer (Wuhan) Research and Development Co. Ltd.
- Pfizer AB
- Pfizer Advanced Pharmaceutical Company Limited
- Pfizer Africa & Middle East for Pharmaceuticals, Veterinarian Products & Chemicals S.A.E.
- Pfizer Afrique de L'Ouest
- Pfizer AG
- Pfizer Anti-Infectives AB
- Pfizer ApS
- Pfizer AS
- Pfizer Asia Manufacturing Pte. Ltd.
- Pfizer Asia Pacific Pte Ltd.
- Pfizer Australia Holdings B.V.
- Pfizer Australia Holdings Pty Limited

- Pfizer Australia Investments Pty Ltd
- Pfizer Australia Pty Ltd
- Pfizer B.V.
- Pfizer Baltic Holdings B.V.
- Pfizer BH D.o.o.
- Pfizer Biofarmacéutica, Sociedade Unipessoal Lda
- Pfizer Biologics (Hangzhou) Co. Ltd
- Pfizer Biologics Ireland Holdings Limited
- Pfizer Biopharma Egypt Import LLC
- Pfizer Biopharmaceuticals Egypt LLC
- Pfizer Biossimilares Participações Ltda.
- Pfizer Bolivia S.A.
- Pfizer Canada ULC / Pfizer Canada SRI
- Pfizer Chile S.A.
- Pfizer Cia. Ltda.
- Pfizer Colombia Spinco I LLC
- Pfizer Commercial Holdings TRAE Kft.
- Pfizer Commercial TRAE Trading Kft.
- Pfizer Consumer Healthcare
- Pfizer Corporation Austria Gesellschaft m.b.H.
- Pfizer Corporation Hong Kong Limited
- Pfizer Corporation S. de R.L.
- Pfizer Costa Rica PFE, Sociedad de Responsabilidad Limitada
- Pfizer Croatia d.o.o.
- Pfizer Deutschland GmbH
- Pfizer Development LP
- Pfizer Development Services (UK) Limited
- Pfizer Dominicana PFE, SRL
- Pfizer Dominicana, S.R.L
- Pfizer East India B.V.
- Pfizer Eastern Investments B.V.
- Pfizer Egypt S.A.E.
- Pfizer Enterprise Holdings B.V.
- Pfizer Enterprises LLC
- Pfizer Enterprises SARL
- Pfizer ESP Pty. Ltd.
- Pfizer Established Medicine Italy S.r.l.
- Pfizer EU PFE MA EEIG
- Pfizer Europe Finance B.V.
- Pfizer Europe MA EEIG
- Pfizer Export B.V.
- Pfizer Export Company
- Pfizer Export Holding Company B.V

- Pfizer Finance Share Service (Dalian) Co., Ltd.
- Pfizer Financial Services
- Pfizer France International Investments
- Pfizer Free Zone Panama, S. de R.L.
- Pfizer GEP, S.L.
- Pfizer Global Holdings B.V.
- Pfizer Global Supply Japan Inc.
- Pfizer Global Trading
- Pfizer Group Luxembourg SARL
- Pfizer Gulf FZ-LLC
- Pfizer H.C.P. Corporation
- Pfizer Health AB
- Pfizer Health Solutions Inc.
- Pfizer Healthcare India Private Limited
- Pfizer Healthcare Ireland
- Pfizer Hellas, A.E.
- Pfizer Himalaya Holdings Coöperatief U.A.
- Pfizer Holding France
- Pfizer Holding Ventures
- Pfizer Holdings Corporation
- Pfizer Holdings Europe Unlimited Company
- Pfizer Holdings G.K.
- Pfizer Holdings International Corporation
- Pfizer Holdings International Luxembourg (PHIL) SARL
- Pfizer Hungary Holdings TRAE Kft.
- Pfizer Ilaclari Limited Sirketi
- Pfizer Innovations AB
- Pfizer Innovations LLC
- Pfizer Innovative Supply Point International BVBA
- Pfizer International LLC
- Pfizer International Markets B.V.
- Pfizer International Operations
- Pfizer International S. de R.L.
- Pfizer International Trading (Shanghai) Limited
- Pfizer Investment Capital Unlimited Company
- Pfizer Investment Co. Ltd.
- Pfizer Investment Holdings S.a.r.l.
- Pfizer Ireland Investments Limited
- Pfizer Ireland PFE Holding 1 LLC
- Pfizer Ireland PFE Holding 2 LLC
- Pfizer Ireland Pharmaceuticals
- Pfizer Ireland Ventures Unlimited Company
- Pfizer Italia S.r.l.

- Pfizer Italy Group Holding S.r.l.
- Pfizer Japan Inc.
- Pfizer Laboratories Limited
- Pfizer Laboratories PFE (Pty) Ltd
- Pfizer Leasing Ireland Limited
- Pfizer Leasing UK Limited
- Pfizer Limitada
- Pfizer Limited
- Pfizer LLC
- Pfizer Luxco Holdings SARL
- Pfizer Luxembourg Global Holdings S.à r.l.
- Pfizer Luxembourg SARL
- Pfizer Manufacturing Austria G.m.b.H.
- Pfizer Manufacturing Belgium N.V.
- Pfizer Manufacturing Deutschland GmbH
- Pfizer Manufacturing Deutschland Grundbesitz GmbH & Co. KG
- Pfizer Manufacturing Holdings LLC
- Pfizer Manufacturing Ireland Unlimited Company
- Pfizer Manufacturing LLC
- Pfizer Manufacturing Services
- Pfizer MAP Holding, Inc.
- Pfizer Medical Technology Group (Belgium) N.V.
- Pfizer Medicamentos Genericos e Participacoes Ltda.
- Pfizer Mexico Holding 2 B.V.
- Pfizer Mexico Holding B.V.
- Pfizer Mexico Luxco SARL
- Pfizer Mexico, S.A. de C.V.
- Pfizer Middle East for Pharmaceuticals, Animal Health and Chemicals S.A.E.
- Pfizer Namibia (Proprietary) Limited
- Pfizer New Zealand Limited
- Pfizer Norge AS
- Pfizer North America Services LLC
- Pfizer OFG Germany GmbH
- Pfizer OFG UK Limited
- Pfizer OTC B.V.
- Pfizer Overseas LLC
- Pfizer Oy
- Pfizer Pakistan Limited
- Pfizer Parke Davis (Thailand) Ltd.

- Pfizer Parke Davis Sdn. Bhd.
- Pfizer Parke Davis, Inc.
- Pfizer PFE ApS
- Pfizer PFE AsiaPac Holding B.V.
- Pfizer PFE Australia Holding B.V.
- Pfizer PFE Australia Pty Ltd
- Pfizer PFE Belgium SPRL
- Pfizer PFE CIA. Ltda.
- Pfizer PFE Colombia Holding LLC
- Pfizer PFE Croatia Holding B.V.
- Pfizer PFE Eastern Investments B.V.
- Pfizer PFE Finland Oy
- Pfizer PFE France
- Pfizer PFE Global Holdings B.V.
- Pfizer PFE İlaçları Anonim Şirketi
- Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V.
- Pfizer PFE Korlátolt Felelősségű Társaság
- Pfizer PFE Limited
- Pfizer PFE Mexico Holding 3 LLC
- Pfizer PFE Norway Holding S.à r.l.
- Pfizer PFE Peru Holding LLC
- Pfizer PFE Peru S.R.L.
- Pfizer PFE Pharmaceuticals Israel Holding LLC
- Pfizer PFE Pharmaceuticals Israel Ltd.
- Pfizer PFE PILSA Holdco S.à r.l.
- Pfizer PFE Private Limited
- Pfizer PFE S.R.L
- Pfizer PFE Service Company Holding B.V.
- Pfizer PFE Servicios Mexico, S. de R.L. C.V.
- Pfizer PFE Singapore Holding B.V.
- Pfizer PFE Singapore Pte. Ltd.
- Pfizer PFE Spain B.V.
- Pfizer PFE Spain Holding, S.L.
- Pfizer PFE Switzerland GmbH
- Pfizer PFE Turkey Holding 1 B.V.
- Pfizer PFE Turkey Holding 2 B.V.
- Pfizer PFE UK Holding 4 LP
- Pfizer PFE US Holdings 4 LLC
- Pfizer PFE US Holdings 5 LLC
- Pfizer PFE, spol. s r.o.
- Pfizer Pharm Algerie
- Pfizer Pharma GmbH
- Pfizer Pharma PFE GmbH

- Pfizer Pharmaceutical (Wuxi) Co., Ltd.
- Pfizer Pharmaceutical Trading Limited Liability Company (a/k/a Pfizer Kft. or Pfizer LLC)
- Pfizer Pharmaceuticals Global B.V.
- Pfizer Pharmaceuticals Israel Ltd.
- Pfizer Pharmaceuticals K.K.
- Pfizer Pharmaceuticals Korea Limited
- Pfizer Pharmaceuticals LLC
- Pfizer Pharmaceuticals Ltd.
- Pfizer Pharmaceuticals Science and Technology Co., Ltd.
- Pfizer Pharmaceuticals Tunisie Sarl
- Pfizer Pigments Inc.
- Pfizer Polska Sp. z.o.o.
- Pfizer Prev - Sociedade de Previdencia Privada
- Pfizer Private Limited
- Pfizer Production LLC
- Pfizer Products Inc.
- Pfizer Products India Private Limited
- Pfizer R&D Holding B.V.
- Pfizer R&D Japan G.K.
- Pfizer R&D UK Limited
- Pfizer Research (NC), Inc.
- Pfizer Romania SRL
- Pfizer S.A.
- Pfizer S.A. (Belgium)
- Pfizer S.A.S.
- Pfizer S.G.P.S. Lda.
- Pfizer S.r.l.
- Pfizer S.R.L.
- Pfizer Saidal Manufacturing
- Pfizer Saudi Limited
- Pfizer Service Company BVBA
- Pfizer Service Company Ireland Unlimited Company
- Pfizer Services 1
- Pfizer Services LLC
- Pfizer Shared Services Unlimited Company
- Pfizer Shareholdings Intermediate SARL
- Pfizer Singapore Holding Pte. Ltd.
- Pfizer Singapore Trading Pte. Ltd.
- Pfizer Specialities Ghana
- Pfizer Specialties Limited
- Pfizer SRB d.o.o.
- Pfizer Strategic Investment Holdings LLC

- Pfizer Trading Polska sp.z.o.o.
- Pfizer TRAE Holdings Kft.
- Pfizer Transactions C.V.
- Pfizer Transactions Ireland Unlimited Company
- Pfizer Transactions LLC
- Pfizer Tunisie SA
- Pfizer Upjohn Hong Kong Limited
- Pfizer Upjohn Korea Limited
- Pfizer Upjohn Management Co., Ltd.
- Pfizer Upjohn Medical Trading Co., Ltd.
- Pfizer Upjohn Medical Trading Co., Ltd. Guangzhou Branch
- Pfizer Vaccines LLC
- Pfizer Venezuela, S.A.
- Pfizer Venture Investments LLC
- Pfizer Ventures (US) LLC
- Pfizer Ventures LLC
- Pfizer Worldwide Services Unlimited Company
- Pfizer Zona Franca, S.A.
- Pfizer, Inc.
- Pfizer, S.A.
- Pfizer, S.A. de C.V.
- Pfizer, S.L.
- Pfizer, spol. s r.o.
- Pharmacia & Upjohn Company LLC
- Pharmacia & Upjohn Company, Inc.
- Pharmacia & Upjohn LLC
- Pharmacia & Upjohn, S.A. de C.V.
- Pharmacia Brasil Ltda.
- Pharmacia Hepar LLC
- Pharmacia Holding AB
- Pharmacia Inter-American LLC
- Pharmacia International B.V.
- Pharmacia Limited
- Pharmacia LLC
- Pharmacia Nostrum, S.A.
- PHIVCO Corp.
- PHIVCO Holdco S.à r.l.
- PHIVCO Luxembourg S.à r.l.
- PIMB OFG Spain Holding, S.L.
- PRISM Holdings B.V.
- PT. Pfizer Indonesia
- PT. Pfizer Parke Davis
- Purepac Pharmaceutical Holdings LLC

- PZR Ltd.
- Renrall LLC
- Rinat Neuroscience Corp.
- Roerig Produtos Farmaceuticos, Lda.
- Roerig S.A.
- Roerig, S.A.
- Sao Cristovao Participacoes Ltda.
- Searle Laboratorios, Lda.
- Servicios P&U, S. de R.L. de C.V.
- Shiley LLC
- Sinergis Farma-Produtos Farmaceuticos, Lda.
- Site Realty, Inc.
- Solinor LLC
- Sugen LLC
- Tabor LLC
- The Pfizer Incubator LLC
- Therachon AG
- Therachon Holding AG
- Therachon SAS
- Thiakis Limited
- Upjohn (Thailand) Limited
- Upjohn Belgium B.V.
- Upjohn Canada ULC / Upjohn Canada SRI
- Upjohn Europe Holdings B.V.
- Upjohn Export B.V.
- Upjohn Global Holdings B.V.
- Upjohn Group Holdings B.V.
- Upjohn Hellas Pharmaceutical Limited Liability Company
- Upjohn Inc.
- Upjohn Intermediate Holdings B.V.
- Upjohn International Holdings B.V.
- Upjohn Laboratorios Lda.
- Upjohn Manufacturing Ireland Unlimited Company
- Upjohn Netherlands B.V.
- Upjohn Pharmaceuticals Inc.
- Upjohn PR Holdings C.V.
- Upjohn PRISM B.V.
- Upjohn South Africa
- Upjohn UK 2 Ltd.
- Upjohn US 1 LLC
- Upjohn US 2 LLC
- Upjohn US Employment Inc.
- Upjohn US Holdings Inc.

- Upjohn Worldwide Holdings Inc.
- US Oral Pharmaceuticals Pty Ltd
- Vicuron Holdings LLC
- Vinci Farma, S.A.
- Warner Lambert del Uruguay S.A.
- Warner Lambert Ilac Sanayi ve Ticaret Limited Sirketi
- Warner-Lambert (Tanzania), Limited
- Warner-Lambert (Thailand) Limited
- Warner-Lambert Company AG
- Warner-Lambert Company LLC
- Warner-Lambert Guatemala, Sociedad Anonima
- Warner-Lambert, S.A.
- Whitehall Laboratories Inc.
- W-L LLC
- Wyeth (Asia) Limited
- Wyeth (Thailand) Ltd.
- Wyeth AB
- Wyeth Ayerst Inc.
- Wyeth Ayerst S.à r.l.
- Wyeth Europa Limited
- Wyeth Farma, S.A.
- Wyeth Holdings LLC
- Wyeth Industria Farmaceutica Ltda.
- Wyeth KFT.
- Wyeth Lederle S.r.l.
- Wyeth Lederle Vaccines S.A.
- Wyeth LLC
- Wyeth Pakistan Limited
- Wyeth Pharmaceuticals FZ-LLC
- Wyeth Pharmaceuticals India Private Limited
- Wyeth Pharmaceuticals Limited
- Wyeth Pharmaceuticals LLC
- Wyeth Prev-Sociedade de Previdencia Privada
- Wyeth Puerto Rico, Inc.
- Wyeth Subsidiary Illinois Corporation
- Wyeth Whitehall Export GmbH
- Wyeth-Ayerst (Asia) Limited
- Wyeth-Ayerst International LLC
- Wyeth-Ayerst Promotions Limited
- Yarra Therapeutics, LLC

**Exhibit D**

**Designation of Trade Secrets and Confidential Information**

Requestor hereby designates the following information as trade secrets and/or confidential information:

- The list of entities controlled or owned by Requestor set forth in Exhibit C.
- All information concerning this request, the request letter itself, the identity of the Requestor, and any other information that could reasonably be used to identify the Requestor.

In accordance with applicable federal law, including 42 C.F.R. § 1008.36(b)(4)(v) and 45 C.F.R. § 5.65, such information shall not be disclosed outside the Government and shall not be duplicated, used or disclosed—in whole or in part—for any purpose other than to evaluate this request.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

## OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201



OFFICE OF COUNSEL TO THE INSPECTOR GENERAL  
330 INDEPENDENCE AVENUE, SW  
COHEN BUILDING - ROOM 5527  
WASHINGTON, DC 20201

September 10, 2019

Jeffrey L. Handwerker  
Arnold & Porter Kaye Scholer LLP  
601 Massachusetts Avenue, NW  
Washington, D.C. 20001-3743

Re: Pfizer Inc.  
Advisory Opinion Request No. R1225

Dear Mr. Handwerker:

We are writing in response to your request for an advisory opinion on behalf of Pfizer Inc., which we received August 26, 2019, regarding creation of a copay assistance program for financially disadvantaged patients being treated for ATTR-CM. In accordance with 42 C.F.R. § 1008.41, we are formally accepting your request as of the date of this letter.

Upon completion of the opinion, you will be notified of any fees owed. In any future correspondence, please refer to reference number R1225. If you have any questions, please feel free to call me at 202.816.9890.

Sincerely,

Stewart W. Kameen  
Senior Counsel  
Industry Guidance Branch



DEPARTMENT OF HEALTH AND HUMAN SERVICES

## OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201



OFFICE OF COUNSEL TO THE INSPECTOR GENERAL  
330 INDEPENDENCE AVENUE, SW  
COHEN BUILDING - ROOM 5527  
WASHINGTON, DC 20201

October 8, 2019

Jeffrey L. Handwerker  
Arnold & Porter Kaye Scholer LLP  
601 Massachusetts Avenue, NW  
Washington, D.C. 20001-3743

Re: Pfizer Inc,  
Advisory Opinion Request No. R1225

Dear Mr. Handwerker:

Pursuant to 42 C.F.R. § 1008.39, we have determined that we need the following additional information to render an informed opinion in connection with the above-referenced request. For the purposes of the questions below, we use the terms as defined by the above-referenced request.

- Please detail how patients would learn about or become aware of the existence of Requestor's Copay Assistance Program for these Medications.
- Please detail how prescribers would learn about or become aware of the existence of Requestor's Copay Assistance Program for these Medications.
- Explain what, if any, talking points, education, or other materials Requestor would furnish to prescribers to instruct them regarding how to communicate with patients regarding the cost of the Medications and any available support from Requestor.
  - Please detail the content of such talking points, education, or other materials, and whether any guidance regarding communications would vary based on the existence or type of the patient's insurance coverage a patient.
- In the development and execution of the Copay Assistance Program, would Requestor use any sort of intermediary that operates between Requestor, prescribers, specialty and other pharmacies, distributors, health plans, and patients, such as a referral hub, a reimbursement hub, a benefits

## Page 2—R1225 Letter to Jeffrey Handwerker

investigations hub, or other third party acting on Requestor's behalf? If so, please describe how such intermediary or intermediaries would support or facilitate the Copay Assistance Program.

- Please detail how patients would learn about or become aware of the "patient support hub" referenced in footnote 30.
- Is the "patient support hub" operated by a third party?
- Please provide additional information about the operations of the "patient support hub" and the information available to patients through that hub.
- What information and documentation would Requestor require prescribers to send to Requestor, or a third party acting on behalf of Requestor, when a patient is directed to the Copay Assistance Program?
- Would Requestor require patients to use a particular specialty pharmacy for acquiring the Medications if they are supported by the Copay Assistance Program?
- What information would be communicated by Requestor, or a third party acting on Requestor's behalf, to the prescriber or pharmacy about the decision to grant assistance to a patient?
- Would the Copay Assistance Program only be open to Federal health care program beneficiaries?
- Requestor mentions its existing "free drug program." Does Requestor plan to offer the Medications for free to any Federal health care program beneficiaries under its existing free drug program? If so, what, if any, criteria would apply to Federal health care program beneficiaries seeking free Medication through the free drug program.
- Please detail any interaction between Requestor's existing free drug program and the Copay Assistance Program. In particular:
  - Would Federal health care program beneficiaries who seek the Medications under the free drug program be redirected to the Copay Assistance Program?
  - Would Federal health care program beneficiaries be denied Medications under the free drug program based on criteria that differs from patients without insurance or with commercial insurance?
  - Would Requestor otherwise take into account a patient's insurance or insurance status in making eligibility determinations for, or as between, the Copay Assistance Program and the free drug program for purposes of the Medications?
- Would the Copay Assistance Program provide support for the other medical needs of patients diagnosed with ATTR-CM, including all prescription drugs used by the patient in connection with managing the disease, treating symptoms of the disease, or treating pain and other side effects of the

## Page 3—R1225 Letter to Jeffrey Handwerker

disease?

- Would the Copay Assistance Program support qualifying ATTR-CM patients' other medical needs regardless of whether the patients are using the Medications?
- Would the Copay Assistance Program support any other drugs or therapies approved by the Food and Drug Administration to treat or manage ATTR-CM and its symptoms and side effects, including drugs and therapies of a competitor that exist now or may exist in the future? If so, please provide detailed information regarding what other drugs or therapies the Copay Assistance Program would support.
- Requestor states on page 12 of its Request that the Medications are "targeted to a Medicare population." What does this statement mean, and why does Requestor target a "Medicare population" with these Medications?
- Requestor refers to "two possible solutions" on page 13. Please confirm that R1225 describes only one proposed arrangement involving the Copay Assistance Program.
- Please confirm that Requestor will determine eligibility according to a reasonable, verifiable, and uniform measure of financial need that would be applied in a consistent manner.
  - Please detail the objective criteria that will be applied uniformly and consistently as part of the financial need determination applied to applicants to the Copay Assistance Program.
- Please provide additional information regarding how the Copay Assistance Program would operate in accordance with the corporate integrity agreement executed by Requestor and HHS-OIG on May 23, 2018.

Additional information should be provided in writing and certified by the same person who certified the initial request to be a true, correct, and complete disclosure of the requested information in a manner equivalent to that described in 42 C.F.R. § 1008.38. See 42 C.F.R. § 1008.39(c). Pursuant to § 1008.39, the time for preparing your advisory opinion will be tolled from the date of this letter until we receive the requested information.

If you have any questions, please feel free to contact me at 202.816.9890 or [Stewart.Kameen@oig.hhs.gov](mailto:Stewart.Kameen@oig.hhs.gov).

Page 4—R1225 Letter to Jeffrey Handwerker

Sincerely,

A handwritten signature in black ink, appearing to read "Stewart W. Kameen". The signature is fluid and cursive, with a large, stylized "S" at the beginning.

Stewart W. Kameen  
Senior Counsel  
Industry Guidance Branch



DEPARTMENT OF HEALTH AND HUMAN SERVICES

## OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201



OFFICE OF COUNSEL TO THE INSPECTOR GENERAL  
330 INDEPENDENCE AVENUE, SW  
COHEN BUILDING - ROOM 5527  
WASHINGTON, DC 20201

October 17, 2019

Jeffrey L. Handwerker  
Arnold & Porter Kaye Scholer LLP  
601 Massachusetts Avenue, NW  
Washington, D.C. 20001-3743

Re: Pfizer Inc.  
Advisory Opinion Request No. R1225

Dear Mr. Handwerker:

Pursuant to 42 C.F.R. § 1008.33, we have determined that we need an expert opinion from the Centers for Medicare & Medicaid Services to render an opinion in connection with the above-referenced request. There will be no fees associated with this expert opinion. Pursuant to 42 C.F.R. § 1008.33(b), the time for preparing your advisory opinion will be tolled from the date of this letter until we receive the expert opinion from the Centers for Medicare & Medicaid Services.

Sincerely,

Stewart W. Kameen  
Senior Counsel  
Industry Guidance Branch